

## REMARKS

### Status of Claims

Claims 11-13, 15-16, and 22-23 are pending in the present application. Claims 14 and 17 are cancelled. Claims 1-10 and 18-21 are withdrawn as directed to a non-elected invention. Claims 11, 13, 15-16, and 22 are amended. Claim 23 is new.

Claims 11 and 22 are amended to specify "administering systemically." This phrase is supported throughout the application as originally filed including the working examples. For instance, the working examples teach that the C-type natriuretic peptide, ("CNP"), transgenic mouse expresses CNP systemically with an elevated CNP blood level, *see also* page 3, paragraph 5 in the originally filed specification. The state of a mouse wherein CNP is expressed in this manner is identical to the state wherein CNP has been systemically administered to the mouse.

Claims 11 and 22 are further amended to specify that "the individual has growth cartilage layers." Support for this phrase is found, for example, on pages 7-8, bridging paragraph, of the originally filed application. This section teaches that individuals encompassed by the invention are free from an FGFR3 abnormality, which is caused by growth inhibition of cartilage bones.

The derivatives as specified in amended claims 11 and 22 are supported, for example, on page 12, paragraph 3 through to page 13, line 17, of the originally filed application. That is, the specification teaches that the derivatives are described in Japanese Patent Publication No. 6-9688A (1994), which corresponds to U.S. Patent No. 5,434,133, and International Publication No. WO 02/074234.

Claim 13 is amended for clarity to specify "or" in lieu of "and/or." Claims 15 and 16 are amended to depend from claim 11. Claim 15 is further amended to cancel the phrase "including humans or birds."

Claim 23 is new. Support for new claim 23 is found throughout the application as originally filed including on page 8, second paragraph.

The claims are amended without prejudice or disclaimer. No new matter is entered by way of this amendment. Reconsideration is respectfully requested.

### **Amendments to the Specification**

As noted above, the instant application is amended to specify that the present application is a national stage application of PCT International Application PCT/JP2005/006837, filed March 31, 2005. The title is also amended to better describe the presently claimed subject matter. In addition, page 12, paragraph 3, of the instant application is amended to specify that Japanese Patent Publication No. 6-9688A corresponds to U.S. Patent No. 5,434,133. No new matter is entered by way of these amendments.

### **Objections to the Specification**

The Examiner objects to the title of the application as allegedly not descriptive of the elected invention. In addition, the Examiner requires that the specification indicate that the present application is a national stage application of PCT/JP05/06837. See Office Action, page 4.

As noted above, the specification is amended according to the Examiner's suggestions. Withdrawal of the objections is respectfully requested.

### **Claim Objections**

Claims 11, 14-17, and 22 are objected to because of the informalities as set forth on page 4 of the outstanding Office Action.

Claims 14 and 17 are canceled. Accordingly, the rejection is moot as to these claims.

Applicants believe that the instant claim amendments obviate the rejections listed in items (1) to (5) on page 4 of the instant Office Action. As noted above, claim 17 is canceled. Accordingly, the rejection described in item (6) of page 4 is moot. Withdrawal of the objections is respectfully requested.

### **Issues under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph**

Claims 11-17 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicants regard as the invention, *see* Office Action, pages 5-6. Specifically, the Examiner states that the claims fail to specify positive method steps, *e.g.*, a step of administration. In addition, the Examiner states that claim 13 is indefinite for specifying the phrase “and/or.” The Examiner further states that claim 15 is indefinite for recitation of the phrase “including humans, or birds.” Applicants respectfully traverse.

As amended, independent claims 11 and 22 specify an administration step. Further, claim 13 is amended to specify “or.” The allegedly unclear phrase in claim 15 is canceled. Accordingly, Applicants believe the rejection is overcome and respectfully request withdrawal.

#### **Issues under 35 U.S.C. § 101**

Claims 11-17 and 22 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter, *see* Office Action, page 6. According to the Examiner, the claims fail to recite particular method steps that require the hand of man.

As noted above, independent claims 11 and 22 are amended to describe an administration step. Accordingly, the claims comply with 35 U.S.C. § 101. Withdrawal of the rejection is respectfully requested.

#### **Issues under 35 U.S.C. § 112, 1<sup>st</sup> paragraph**

##### *Enablement*

##### Basis for the Rejection

Claims 11-17 and 22 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement, *see* Office Action pages 6-12. Specifically, the Examiner asserts that the present application is not commensurate in scope with the instant claims. In particular, the Examiner alleges that the specification does not enable the claimed method wherein the individual does not experience endochondral ossification as a part of growth. According to the Examiner, the specification is directed solely to transgenic mice that experience increased levels of serum CNP continuously throughout growth. The Examiner further alleges that the present application fails to provide examples wherein administration of CNP increases the body height of an adult, (post puberty). In addition, the Examiner asserts that an ordinary artisan would not

have been able to reasonably predict that administration of CNP to a post-pubescent individual would have resulted in an increase in body height.

The Examiner further alleges that the specification only discloses GC-B activators that are CNP peptides. In particular, the Examiner states that the present application fails to provide guidance regarding the selection of other compounds that activate GC-B. The Examiner further asserts that an ordinary artisan would have been able to determine what additional mutations in CNP would have resulted in retention of activity.

#### The Present Invention

Although Applicants do not agree with the Examiner, the claims are amended in an effort to expedite prosecution. As amended, independent claim 11 is directed to a method for increasing a body height of an individual free from fibroblast growth factor receptor 3, (FGFR3) abnormality, comprising administering systemically C-type natriuretic peptide (CNP) or a derivative thereof to increase the body height in the individual, wherein the individual has growth cartilage layers, wherein the derivative comprises a deletion, substitution or addition of between 1 to 10 amino acids in the amino acid sequence of CNP, while possessing a CNP activity, and comprises the following peptide sequence:

(A)-(B)-(C)-Gly-(D)-(E)-(F)-Asp-Arg-Ile-Gly-(G)-(H)-Ser-

(I)-(J)-Gly-(B)-(K)

wherein (A) represents H-, H-Gly, H-Lys-Gly, H-Ser-Lys-Gly, H-Leu-Ser-Lys-Gly, H-Gly-Leu-Ser-Lys-Gly, H-Ser, H-Ser-Ser, H-Arg-Ser-Ser, H-Arg-Arg-Ser-Ser, H-Leu-Arg-Arg-Ser-Ser, or H-Ser-Leu-Arg-Arg-Ser-Ser; (B) represents H-Cys; (C) represents Phe, pCl-Phe, pF-Phe, or Cha; (D) represents Ile, Val, or Leu; (E) represents Lys, Leu, or Met; (F) represents Leu, Ile, Ala, or Val; (G) represents Ser, Gly, Thr, Asn, or Ala; (H) represents Met, Ala, Trp, His, Lys, Ser, Gly, or Gln; (I) represents Gly, Lys, Ala, or Leu; (J) represents Leu or Met; (K) represents -OH, -Asn-OH, -Asn-Ser-OH, -Asn-Ser-Phe-OH, -Asn-Ser-Phe-Arg-OH, or -Asn-Ser-Phe-Arg-Tyr-OH; and the symbol "..." between (B) and (B) represents a disulfide bond.

As amended, claim 22 is directed to a method for extending a cartilage bone free from FGFR3 abnormality in an individual, comprising administering systemically CNP or a derivative

thereof to activate guanyl cyclase B (GC-B) in the individual, wherein the individual has growth cartilage layers, wherein the derivative comprises a deletion, substitution or addition of between 1 to 10 amino acids in the amino acid sequence of CNP, while possessing a CNP activity, and comprises the described peptide sequence.

The specification enables the instant claims

As amended, the claims specify that the individual to whom CNP or a derivative thereof is administered has growth cartilage layers, *i.e.*, the individual is not a post-puberty individual. Further, the CNP transgenic mice described in the present working examples teach that CNP is expressed systemically and that the CNP blood level is elevated. CNP was administered systemically to the model mice described in the working examples. The described results show that the total thickness of the growth cartilage layers in mice with growth cartilage layers is significantly greater in terms of total thickness in comparison to wild type, which results in an increase in body height, *see* Example 6, Figure 5. In view of the foregoing, the instant claims are adequately supported by the working examples in the present application.

Moreover, the amended claims specify that the GC-B activators are limited to CNP or derivatives thereof, which are described in Japanese Patent Publication No. 6-9688 (1994) and International Publication No. WO 02/074234. Derivatives of CNP-22 are also described in Japanese Patent Publication No. 6-9688 (1994) and International Publication No. WO 02/074234. Accordingly, an ordinary artisan would have recognized at the time of the invention, that the CNP derivatives described in the instant claims would have an effect on GC-B activation.

Furthermore, in response to the Examiner's allegation that the specification fails to provide guidance for the selection of compounds other than CNP for GC-B activation, Applicants direct the Examiner's attention to page 14, first paragraph of the originally filed application. In this section, an assay system that may be used to identify GC-B activators is described. Accordingly, an ordinary artisan would have been able to identify activators of GC-B without undue experimentation.

In view of the foregoing, the claims comply with the enablement requirement. Withdrawal of the rejection is respectfully requested.

*Written Description*

Claims 11-17 and 22 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, *see Office Action*, pages 12-15. Specifically, the Examiner asserts that the claims potentially encompass derivatives with an unlimited number of mutations with respect to CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2, which have CNP activity. According to the Examiner, an ordinary artisan is not able to envision the detailed chemical structure of the encompassed genus of GC-B activators. Accordingly, the Examiner alleges that conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the isolation method.

As noted above, the GC-B activators described in the amended claims are limited to CNP or derivatives thereof as disclosed in Japanese Patent Publication No. 6-9688 (1994) and International Publication No. WO 02/074234. Accordingly, at the time of the invention, Applicants submit that the CNP derivative described in the instant claims were known to activate GC-B. Moreover, CNP and derivatives thereof are sufficiently described on pages 9-14 of the present application.

In view of the foregoing, the claims comply with the written description requirement. Withdrawal of the rejection is respectfully requested.

**Issues under 35 U.S.C. § 102(b)**

Claims 11-17 and 22 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Miyazawa *et al.*, 2002, *Endocrinology* 143(9):3604-3610 ("Miyazawa"), *see Office Action*, pages 15-17. Applicants respectfully traverse.

Miyazawa describes a CNP Tg mouse with targeted expression of CNP in growth plate chondrocytes, *i.e.*, the mouse expresses CNP locally in growth plate chondrocytes. When CNP is locally administered to an individual, extension of cartilage bones due to CNP may occur. However, local administration is not synonymous with systemic administration. Accordingly, Miyazawa cannot be interpreted to teach that systemic CNP administration results in an individual, extension of cartilage bones. That is Miyazawa does not demonstrate this association. Moreover, Applicants wish to emphasize that the model mice employed in the instant application

are distinguishable from those described in Miyazawa. Applicants further submit that promoting the extension of cartilage bones *via* elevating CNP levels in the blood was first demonstrated in the present application. In addition, Applicants submit that an ordinary artisan would not have been able to reasonably predict at the time of the invention from Miyazawa's disclosure, which teaches targeted expression of CNP in CNP Tg mice, that systemic administration of CNP would have resulted in an increase in body height.

In view of the foregoing, Miyazawa does not anticipate the instant claims. Withdrawal of the rejection is respectfully requested.

CONCLUSION

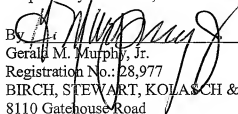
In view of the above amendments and remarks, Applicants believe that the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact L. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

  
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